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THE METABOLITES OF FENTANYL AND ITS DERIVATIVES

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An extensive literature search identified 15 metabolites for the synthetic opiod fentanyl. Sufentanil and alfentanil had 2 and 3 reported metabolites respectively. Factors determining the metabolic fate of these opiods, as well as the nature and quantity of metabolites isolated, are discussed.

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PREFACE

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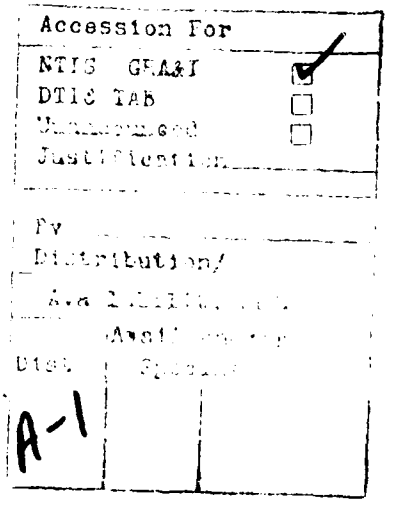

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The Metabolites of Fentanyl and its Derivatives

I. INTRODUCTION

Since its introduction in the 1960's, *fentanyl has found widespread* clinical use as a morphinomimetic narcotic analgesic, primarily in the form of its citrate salt (Sublimaze, Fentanest, Pentanyl). With a potency in rats of almost three hundred times that of morphine, its onset time and duration of action are considerably shorter than that of the naturally occurring opiate. Its safety margin (i.e., the ratio of its therapeutic dose to its lethal dose) is well over 100 in animal studies. In man, its activity is somewhat attenuated, for example, intramuscular administration of fentanyl in clinical studies has led to potency ratio estimates of 50 (relative to morphine).[1] These properties have occasioned its popularity in surgical analgesia, especially when combined with a powerful tranquillizer such as droperidol in the technique of *neuroleptanalgesia*.[2]

Because fentanyl binds to the same central nervous system (CNS) receptors as its progenitor morphine, it possesses many of the undesirable side effects of the venerable old drug first isolated by Serturner in 1806.[3] Respiratory depression, cardiac depression, emesis, and dependence are the more significant liabilities of narcotic analgesics. "Fentanyl rebound," the sudden, often unpredictable onset of respiratory depression, has required the careful monitoring of patients for several hours after

anaesthesia. On the other hand, the exceptional potency of this opioid permits administration of minute doses relative to morphine. Paul A. J. Janssen, fentanyl's discoverer, predicted that this observation results from specific interaction with analgesic receptors, minimizing its binding at unwanted biological sites, which produces side effects. While respiratory depression is troublesome, although handleable, the seminal discovery in the medical profile of fentanyl was that it has minimal effect on cardiac function, occasioning thousands of reports of its use in various types of heart surgery.

In addition to the aforementioned properties, the other remarkable observation is that fentanyl, unlike morphine and every other narcotic analgesic prepared up to that time except etonitazene, is not a 4-phenylpiperidine. Fentanyl is a congener of 4-phenylpiperidine in which the piperidine and phenyl rings are separated by an -NH- group. Its discovery demonstrated that a relatively simple molecule could possess remarkably high potency. Thus, an extremely potent drug could be manufactured at a small fraction of the cost necessary to isolate morphine from dried opium poppies. This fact has not gone unnoticed by makers of illicit drugs and has had dire consequences in the recent appearance of "designer" drugs. These compounds are very close in structure to fentanyl but have not yet been placed on the list of controlled substances. As a result, makers of illicit drugs have pursued this activity to remain one step ahead of drug enforcement authorities.

As expected, pharmaceutrical companies have vigorously pursued Janssen's lead, and synthesized innumerable compounds based on the 4-anilinopiperidine structure in hope of finding compounds whose

pharmacological profiles are even more impressive than that of fentanyl. Of the many derivatives that have been prepared, sufentanil, alfentanil, cis-3-methylfentanyl, and ohmefentanyl are particularly interesting. *Sufentanil* is an order of magnitude more potent than fentanyl and exhibits an unusually high safety margin. *Alfentanil,*[4] less potent than fentanyl, has a faster onset time and a very short duration of action, making it an attractive candidate for brief surgical procedures. According to studies by Janssen and coworkers,[5] *carfentanil* is one of the most powerful, achiral fentanyls. In addition to high potency, *cis-3-methylfentanyl,*[5] *ohmefentanil,*[6,7] and *lofentanil*[5] illustrate the importance of stereoisomerism in determining the potency of this family of opioids. Table 1 lists the analgesic potency of fentanyl and its derivatives.

Table 1. ANALGESIC POTENCY OF SYNTHETIC OPIOIDS

	Relative Potency[a]	
[Morphine]	1.0	0.003
Fentanyl	286	1.0
Sufentanil	1260	4.4
Alfentanil	72	0.25[b]
Carfentanil	7682	27
Lofentanil	5625	20
(+)-cis-3-Methylfentanyl	5431	19
Ohmefentanyl	6300[c]	28[c]
[Pethidine = Meperidine]	0.6	0.02

[a] Van Daele, P.G.H.; De Bruyn, M.F.L.; Boey, J.M.; Sancuk, S., Agten, J.T.M.; and Janssen, P.A.J.; Arneim. Forsch. (Drug Res.), Vol. 26, pp 1521-1531 (1976).

[b] Cookson, R.F.; Niemegeers, C.J.E.; and Vanden Bussche, G.; J. Anaesth., Vol. 5, pp 147S - 155S (1983).

[c] Jin, W.; Xu, H.; Zhu, Y.; Fang, S.; Xia, X.; Huang, Z.; Ge, B.; and Chi, Z.; Scientia Sinica Vol. 24, pp 710 - 720 (1981).

The results of an extensive literature search for the metabolites of fentanyl and its derivatives will be presented. Knowledge of the reported metabolite structures was considered useful for making reasonable predictions for drugs whose metabolites were not determined. The role played by metabolites in the potency, duration of action, respiratory depression, and other physiological effects was also investigated. Presumably, knowledge of the biotransformation pathways of this unique family of opioids provided insight in the design of molecules of greater selectivity and increased safety margins, yet be uncomplicated by unacceptable side effects.

2. IMPORTANT FACTORS IN DETERMINING DRUG METABOLISM

Many factors are important in determining the nature of drug metabolites. It is reasonable to expect some metabolite variation depending on the animal chosen for study. The mode of administration (i.e., intravenous, intramuscular, subcutaneous, etc.) can influence drug metabolism. In addition, the tissue or elimination sample chosen for analysis may influence the metabolite distribution (e. g., the results will probably depend on the organ studied both in terms of the nature and quantity of product isolated). The method of isolation can affect the results, because some compounds are extracted more readily than others. It is also possible that the isolation procedure will fail to isolate labile metabolites. Within a given animal species, metabolism is influenced by age, sex, pregnancy, hepatic disease, hormonal imbalances, diet and diurnal variation. The results of in vivo studies may be different from

those of in vitro studies using tissue homogenates. Finally, significant individual variation has been observed in the identity and quantity of isolated biotransformation products. Two of these factors, administrative mode and isolation method, will be discussed in more detail.

2.1 Administrative Mode.

How the drug is administered defines the position at which the drug enters the cirulatory system. This entry point determines the sequence of organs that are traversed on route to the target organ. Passage through an organ that metabolizes the drug can result in a significant first-pass effect, such that a mixture of the unchanged drug and various quantities of metabolites exit. In the case of opioids, it is the central nervous system that must be accessed for the most significant effects to be expressed; the blood-brain barrier must be crossed. Those modes of administration that lead to metabolic transformation, and production of more polar metabolites, which are unable to pass the blood-brain barrier, could lead one to overlook useful pharmacological properties. These properties would be observed if an administrative route exposes the drug directly to the blood-brain barrier without extensive exposure to metabolizing organs.

2.2 Isolation Methods.

Most researchers studying the metabolism of fentanyl and other

xenobiotics have been concerned primarily with the characterization and not the quantitation of metabolites. Several troublesome questions can be posed interpreting some of the results in the literature. Most nettlesome of all is the almost uniform failure of researchers to consider chemical transformation of metabolites during extraction, concentration, chromatography, etc. This can be understood, in part, if one considers the vanishingly small quantities of material that the therapeutic dose of these 4-anilinopiperidines represent. The methods chosen for isolation and identification must be extremely sensitive due to the small quantity of these drugs that are administered. Higher doses, which would simplify isolation, may fall over the toxicity threshold.

In a study by McClain,[26] toluene extracts of urine from male humans was followed by paper chromatography. A preponderance of unchanged fentanyl and small quantitites of metabolites that had Rf values different than those of **1**, **2**, or **15** were obtained. These results demonstrate the presence of compounds other than those looked for. It has not been shown, however, that **1**, **2**, or **15** are not metabolites. In order for this statement to be true, it must be demonstrated that these compounds can be extracted from urine in reasonable concentrations using toluene. Appropriate control experiments were either, not run, or not reported.

Concentration of extracts of biological samples can produce ambiguities. van Rooy and coworkers[20] suggest that Maryama's[9] failure to detect **1** in their metabolic studies with rats may be due to the volatility of **1** and could well have been lost during evaporation of the extraction solvent, $CHCl_3$.

Metabolites that contain acidic or basic functional groups can be quite soluble in the aqueous samples that are extracted in certain pH ranges. To increase the likelihood of a complete extraction, the pH should be adjusted so that an acid, neutral, and basic extract is obtained. Possible metabolite lability at certain pH ranges must be considered. Conjugation can lead to water-soluble derivatives that resist complete extraction; it is prudent to treat the samples with ß-gluconidase and sulfatase to liberate the metabolites from their conjugates.

A problem implicit in identification of metabolites in urine and feces is that these samples are pooled from a large number of possible tissue sources. Thus, the question of where the compound was produced, as well as whether this product is a primary or secondary metabolite, cannot be addressed. Certain metabolites that reach these elimination products may not survive the storage time prior to isolation.

3. METABOLISM OF FENTANYL AND ITS DERIVATIVES

Fentanyl is a polyfunctional molecule that has many possible sites for metabolic transformation. It is a heterocyclic tertiary aliphatic amine that contains two different phenyl rings, as well as a disubstituted aromatic amide. Tertiary aliphatic amines undergo biotransformation to the tertiary amine oxides, however, the reaction is reversible, and it is sometimes difficult to establish the occurrence of this metabolic pathway. Tertiary amines also undergo N-dealkylation, a process that occurs through the carbinolamine. When this process occurs on the

phenethyl side chain, secondary amine **I** is produced in addition to phenylacetaldehyde that is readily oxidized to phenylacetic acid. Oxidation at the 2-position of the piperidine ring produces a carbinolamine, which upon transformation to the more stable aminoaldehyde results in ring cleavage.

Aromatic rings are known to undergo oxidation to produce the corresponding phenolic derivatives (**6**, **12**, **7**). In addition, benzylic positions are particularly susceptible to oxidation (**12**, **13**). Amide functions typically undergo hydrolysis (**2**), and oxidation of the carbon chain (**9**, **10**) is also common.

Alfentanil and sufentanil would be expected to undergo O-de-methylation, producing 4-hydroxymethyl derivatives. As is the case with fentanyl, oxidative N-dealkylation at the heterocyclic nitrogen is anticipated, as is hydrolysis of the amide linkage.

This discussion considers only competing reactions of monofunctional moieties and does not consider the possibility of interactions between two or more of fentanyl's functional groups in determining the biotransformation products. In addition, only Phase 1 reactions (i.e., those that concern the primary transformation of functional groups (oxidation, hydrolysis, reduction, etc.) as opposed to condensation reactions with polar molecules such as glucuronic acid or sulfate ion to provide conjugates (Phase 2 reactions)) are considered.

The literature search results for the metabolites of fentanyl and its derivatives are listed in Table 2.

Table 2. FENTANYL METABOLITES

In Vivo Studies

Animal	Sex	Mode	Sample	Technique	Recovery	Metabolites	Reference
Rat	M	IV	Urine	Radioisotope	80%	**1**(52%) **6** and/or **7** (2%)	7
			Feces			**1**(19%)	
"	F	SC	Urine	Extraction TLC/MS/GC	-	**2**	8
"	M	PO	Urine	Stable Isotope GC/MS	-	**1, 5, 11** **3** and/or **4** **9** and/or **10**	9
		IV	Urine	"		*(same as above)*	
"	M	PO	Urine	Stable Isotope GC/MS	-	**1, 4, 5, 6** (para), **10, 13, 14,** + unident. metab.	10
"	F	IV	Organs[a]	Radioisotope HPTLC	-	**1, 2, 6** (para),11 **7** (para)?, **12, 15**	
"	M	IV	Organs[b]	Radioisotope TLC	-	**1, 6** + three 12 unident. metab.	
		IM	Urine	"	56%	**1, 6** + three unident. metab.	
			Feces		7%	**1, 6**	

[a]Brain, liver, kidneys, adipose tissue, lungs, muscle, stomach
[b]Brain, liver, stomach, small intestines, kidney, lungs, myocardium, adipose tissue, skeletal muscle

Table 2. FENTANYL METABOLITES (continued)

Animal	Sex	Mode	Sample	Technique	Recovery	Metabolites	Reference
Guinea Pig	M	PO	Urine	Stable Isotope GC/MS	_	**6** (para) + two unident. metab.	10
Rabbit	M+F	IV	Urine/Bile	Radioisotope TLC	27% (5 h)	unidentified	13
		IM			4%	"	
Dog	-	IV	Urine	Radioisotope Paper chromat.	32% (6 h)	≥ two unidentified metab.	14
"	-	IV	Urine			**2**	15
Horse	M	IV	Urine	Radioisotope TLC	80%	**816**	
"	M	IV	Urine	RIA	90%	**8**	17
Man	-	IV	Urine	-	-	**6** (para)	10
"	M+F	IV	Urine	Stable Isotope	59%	**1** (26-55%) **3** and/or **4** **9** and/or **10**	18
"	-	IV	Plasma	GC; MS	-	**1, 2**	19
"	M+F	IV	Urine	RIA	15-20%	-	20
"	M	IV	Urine	Paper chromat. 72 h Radioisotope	76%	unidentified	21
			Feces		9%		
"	M+F	IV	Urine	Radioisotope	67% (4 d)	-	22

Table 2. FENTANYL METABOLITES (continued)

In Vitro Studies

	Technique	Recovery	Metabolites	Reference
Hepatocytes (Rat)	Stable Isotope GC/MS	_	**1,5,10,13,14** **6**(meta,para) and/or **12**	10
Hepatocytes (Guinea Pig)	Stable Isotope GC/MS	-	**1, 5, 6** (para), **6**(meta,para) and/or **12** **10,13,14**	10
Tissue homogenates (Mouse)	Radioisotope TLC	60 - 80%	**1** + four unidentified metab.	23
Tissue homogenates (Rat)	Radioisotope TLC	-	**1, 6** (para) + three unidentifed metab.	12

OTHER FENTANYLS

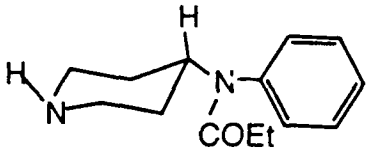
Sufentanil

rat; dog		**16, 17**	24

Alfentanil

rat; dog		**6,18,19**	25

Table 2. FENTANYL METABOLITES (continued)



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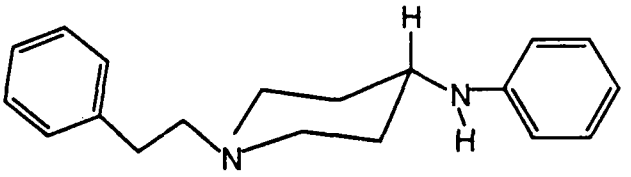

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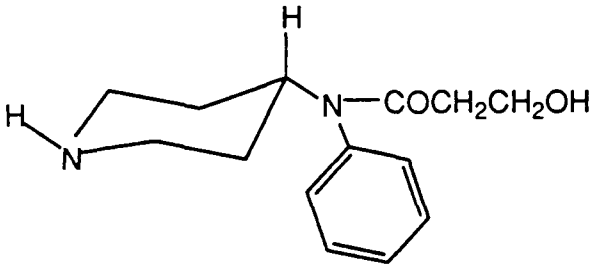

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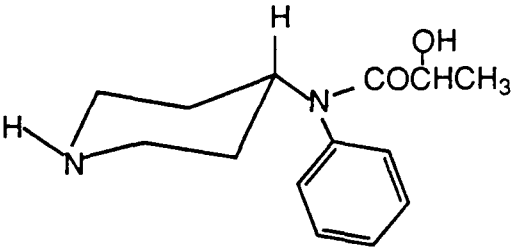

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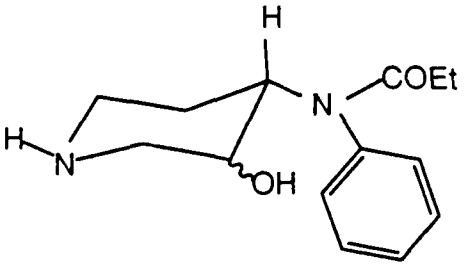

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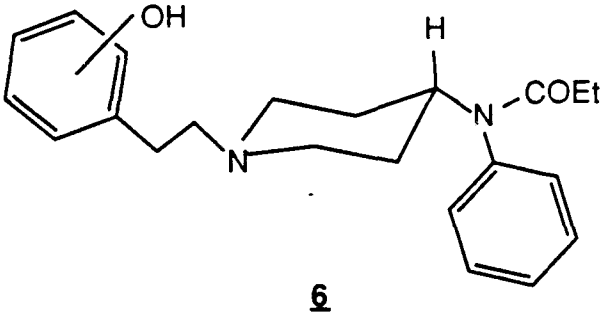

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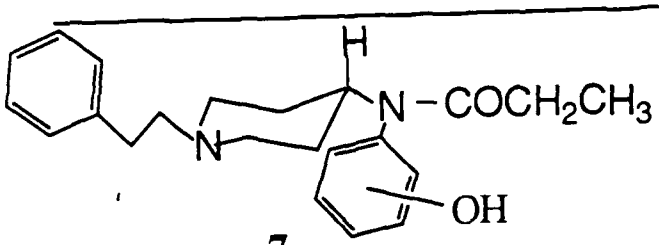

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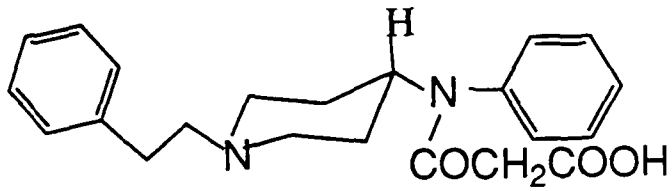

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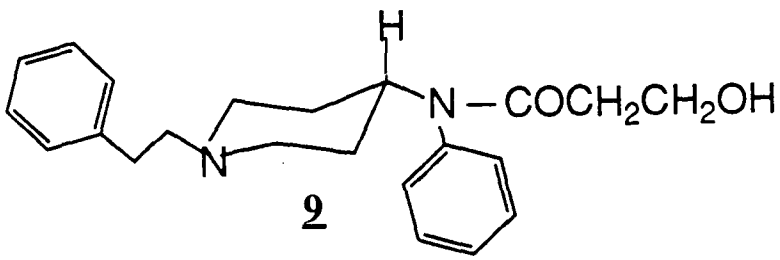

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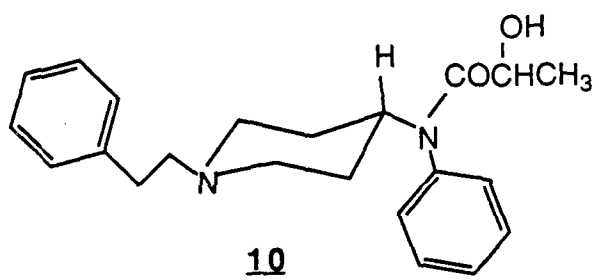

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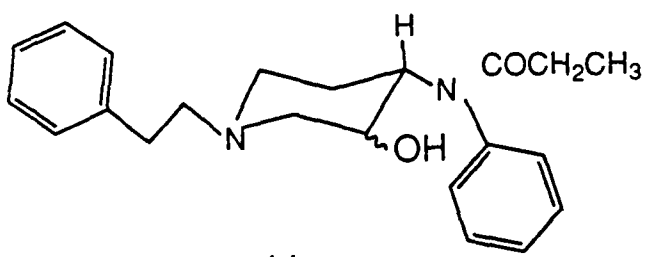

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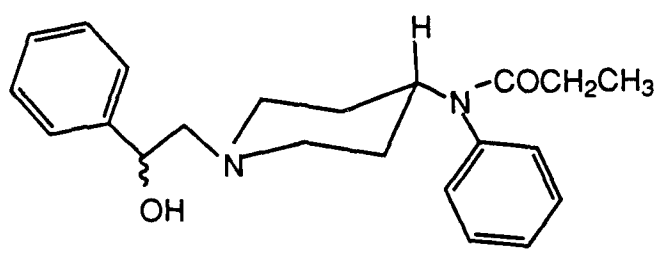

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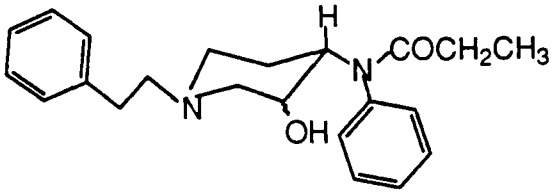

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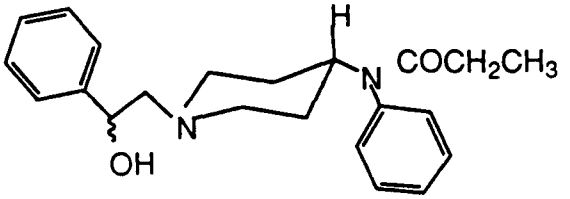

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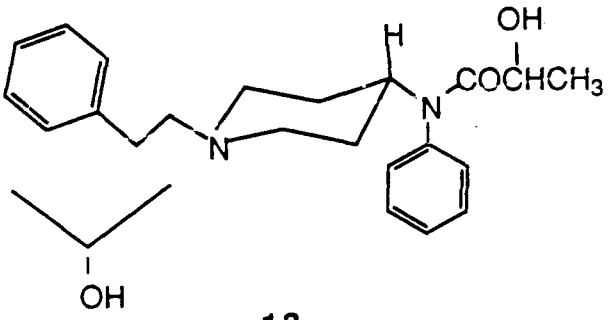

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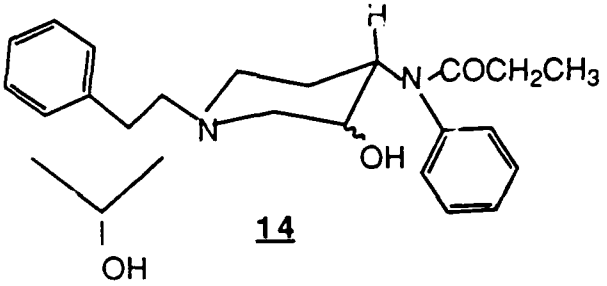

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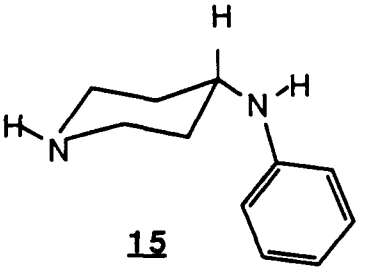

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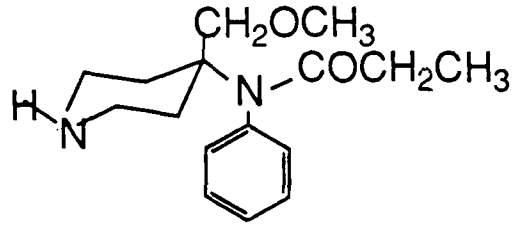

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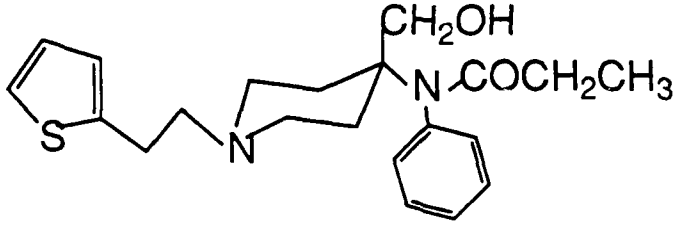

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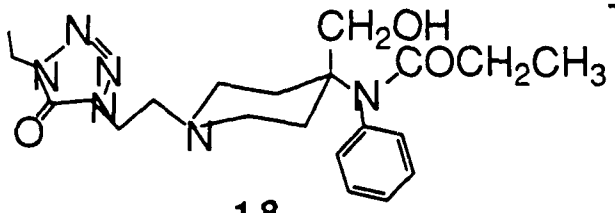

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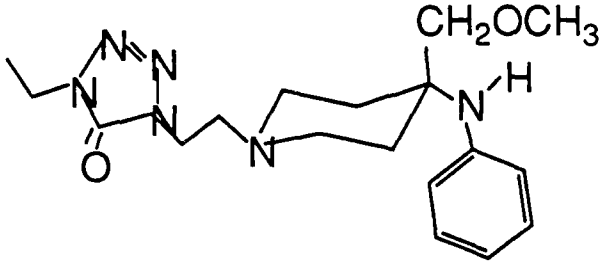

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4. ANALYTICAL TECHNIQUES

4.1 Stable Isotopes.[31,32]

The drug is synthesized with deuterium atoms substituted at a specific position or positions. After administration and recovery of the drug and its metabolities, the gas chromatographic/mass (gc/ms) spectral data are collected. Goromaru and coworkers,[10,11] for example, prepared the deuterated fentanyl derivative in which the anilino moiety was completely substituted by deuterium (a pentadeuterium derivative.) Equimolar quantities of the labelled and unlabelled compound were administered to the animals, metabolized samples were isolated and analyzed by gc/ms after conversion to the trimethylsilyl derivatives to increase volatility. Those compounds of the mixture whose mass spectra contain doublets, separated by 5 amu due to the pentasubstitution, clearly originated from the administered drug. It should be obvious that those biotransformation products that do not contain the anilino function cannot be identified directly using this procedure. A knowledge of the general metabolic routes, however, usually allows one to infer the structures of the unlabelled metabolites. Confirmation of the identity of these materials is possible if one labels another part of the parent drug molecule. In the example given above, it would be desirable to prepare and administer the pentadeuteriophenylethyl derivative and proceed as described above. Perhaps the most versatile compound for studies of fentanyl metabolism is the compound in which the piperidine ring is perdeuterated; undoubtedly, synthetic difficulties have hitherto frustrated the use of this compound in metabolic studies of fentanyl.

This analytical technique has several advantages. Deuterium is not radioactive and studies of this type can be applied to human subjects. The power of gas chromatographic separation is combined with the structural assignment capability of mass spectral fragmentation patterns. The presence of "clusters" in the mass spectrum allows rapid recognition of metabolites. Disadvantages arise whenever the required deuterated compounds are difficult to synthesize, the metabolites are nonvolatile, and cannot be readily converted to volatile derivatives, and when primary and secondary deuterium isotope effects[33] impugn the assumption of identical behavior for labelled and unlabelled drugs.

4.2 Radioisotope Tracers.

The drug is synthesized incorporating a radioisotope, usually tritium (^{3}H) or carbon 14 (^{14}C). For fentanyl, the label is normally placed in one of the two aromatic rings. This technique, like the stable isotope technique, allows one to identify metabolites that are normally found in bodily fluids, such as phenylacetic acid. It suffers also from the fact that metabolites can only be identified directly if they contain that portion of the original drug molecule that contained the isotopic substitution. It is thus necessary to use drug molecules that contain labels in different portions of the molecule, or to place the label at a position where any metabolic transformation is likely to lead to retention of the label, for example, by labelling the piperidine ring of the fentanyl derivative. Regiotopic labelling of the parent drug molecule can be quite challenging.

When combined with the isotope dilution technique, the level of radioactivity can be kept minimal, and the method is innocuous enough to be used with human subjects. The total recovery is conveniently determined from the total recovered radioactivity relative to the administered dose. In addition, due to the sensitivity of the method of detection, minute quantities of the material can be recognized on separation techniques such as analytical thin layer chromatography (tlc).

4.3 Radioimmunoassay.

Radioimmunoassay (RIA) is a technique in which the concentration of the drug is determined from its inhibitory effect on the binding of the radiolabelled drug to a measured quantity of antibody by addition of known concentrations of the unlabelled drug. After incubation, the bound and free forms of the drug are separated, and the concentration of the drug is determined from a standard curve that is derived using the antisera and known concentrations of the drug.

In studies of Henderson[18] and Schleimer,[21] fentanyl is rendered antigenic by synthesis of the immunogen, carbosyfentanylbovine gamma globulin conjugate. Succinic anhydride was reacted with N-1-(2-phenylethyl)- 4-phenylaminopiperidine to produce carboxyfentanyl [N-1-(2-phenylethyl)-4-piperidyl-N-phenyl-3-carboxypropanamide]. Reaction with bovine gamma globulin in the presence of a carbodiimide produced the immunogen. Rabbits were immunized by intradermal and subcutaneous injection. Blood samples were collected and the sera

separated. Control sera were obtained from rabbits that had been immunized with the coat protein of the tobacco mosaic virus. Antisera at various concentrations were reacted with a known quantity of tritium-labelled fentanyl. Globulins were precipitated, sedimented and washed, and the association constants for fentanyl with antibodies were determined.

RIA has the advantage of high sensitivity, and samples can normally be handled without extraction or concentration. It depends, however, on the assumption that the antibodies are specific for the compound to be determined. The magnitude of cross reactivity must be determined for each compound that might be present in the sample.

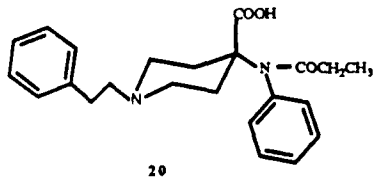
5. INFLUENCE OF METABOLITES ON PHARMACOLOGICAL ACTIVITY

There is no evidence at present to indicate that the metabolites of fentanyl are more potent than the parent drug. In a recent study[27], the results of a comparison of fentanyl levels obtained by radioimmunoassay and radioreceptor assay in patient sera provided no evidence for active metabolites. In direct administration of the drugs themselves, metabolites **1**,[2,28] **2**,[2,28] **6**(ortho),[29] and **6** (meta)[29] have been found to be inactive. Goromaru and coworkers,[11] Schneider[12] and Lehmann[13] have detected **6** (para) in their metabolic studies; this oxidation product was found to have a potency of only 0.9% that of fentanyl in rats.[30] Although

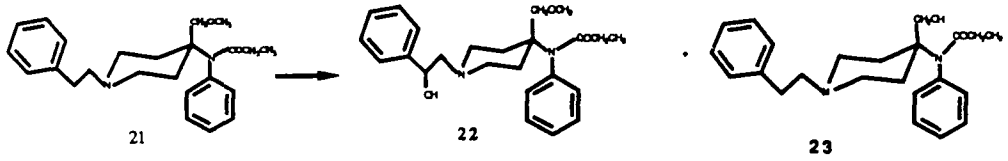
lower than that of fentanyl, the activity of **12**, which was suggested as a possible metabolite by Goromaru[11] and later identified in rats by Schneider,[12] has about one-fifth the potency of the parent drug. The activity of the remaining metabolites is unknown. For metabolites **5**, **11**, and **14**, stereoisomerism (two enantiomeric pairs of diastereomers for each metabolite) is possible. The stereochemistry of the metabolites has not been reported undoubtedly due to the difficulty of assigning structures to the vanishingly small quantities of material that have been detected, as well as the syntheses of these materials in optically active form would be quite challenging.

The results of metabolic studies of carfentanil are not reported to date. Based on knowledge of the metabolic transformations of these compounds, it is not unreasonable to predict metabolic products. A reasonable metabolite for carfentanil, formed by hydrolysis of the ester functionality, is **20.** This compound has been prepared by Van Daele et al.[5] and was found to be inactive.

It is interesting to speculate on the metabolism of other fentanyls based on the findings for fentanyl. Compound **21** is reported by van Daele (1976) to have 14 times the potency of fentanyl. Metabolic oxidation at the benzylic position produces a compound, **22**, that maintains much of the original activity (10 times that of fentanyl.) O-Dealkylation produces **23** that is 1.5 times as active as fentanyl.



20



21 22 23

Chemical Structures

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